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Thiosugars. VII.[1] Synthesis of Methyl 2,3,5,6-Tetradeoxy-2,3,5,6-tetrathio-β-L-galactofuranoside and -α-D-Altrofuranoside

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The 5,6-dimethanesulfonyl derivative (**2**) of methyl 2,3-di-S-benzyl-2,3-dideoxy-2,3-dithio-α-D-altrofuranoside (**1**) reacted with sodium ethyl xanthate to give methyl 2,3-di-S-benzyl-2,3,5,6-tetradeoxy-2,3-dithio-5,6-(thiocarbonyl) dithio-β-L-galactofuranoside (**3**) and -α-D-altrofuranoside (**4**). Reduction of **3** and **4** with liquid ammonia-metallic sodium gave methyl 2,3,5,6-tetradeoxy-2,3,5,6-tetrathio-β-L-galactofuranoside (**5**) and -α-D-altrofuranoside (**6**), respectively.

Keywords——potassium ethyl xanthate; NMR; configuration; chemical shift; 2,3,5,6-tetrathio sugar; 5,6-trithiocarbonyldithiofuranoside; α-D-altrofuranoside; β-L-galactofuranoside

Recently, we have been investigating the introduction of thiol groups into sugars.[3] Replacement of hydroxy groups in sugars with thiol groups is not only of synthetic interest but may also affect the physiological activity. We report here on the synthesis of methyl 2,3,5,6-tetradeoxy-2,3,5,6-tetrathio-β-L-galactofuranoside and -α-D-altrofuranoside.

In order to convert methyl 2,3-di-S-benzyl-2,3-dideoxy-2,3-dithio-α-D-altrofuranoside[4] (**1**) to the 2,3,5,6-tetrathio sugar, the reaction of the 5,6-dimethanesulfonyl derivative (**2**) of **1** with potassium thiocyanate was attempted by analogy with the treatment of the 4,6-di-O-methanesulfonyl derivative of glucose with potassium thiocyanate to introduce sulfur.[5] However, treatment under various conditions was unsuccessful. Accordingly, we attempted to react **2** with sodium trithiocarbonate by a modification of the synthetic method for thioctic acid by Komori *et al.*[6] Yellow crystals (**3**) and a yellow syrup (**4**) were isolated by silica gel column chromatography in a ratio of 1:5 (total yield; 23%). Their structures were assigned as 5,6-trithiocarbonate on the basis of spectroscopic evidence. The circular dichroism (CD), optical rotatory dispersion (ORD), and ultraviolet (UV) absorptions (see "Experimental") of **3** and **4** were very similar. The UV spectra showed absorption bands[7,8] at 318 and 440 nm, characteristic of the trithio group. The similar elemental analysis for **3** and **4**, which were consistent with a methyl 2,3-di-S-benzyl-2,3,5,6-tetradeoxy-2,3-dithio-5,6-(thiocarbonyl)dithiofuranoside structure, indicated that **3** and **4** are epimeric at C-5.

The mechanism of formation of the trithiocarbonate compound from the mesyl derivative (**2**) with sodium trithiocarbonate presumably involves episulfide intermediates. The mechanism of formation of trithiocarbonate compounds from epoxides or episulfides with potassium

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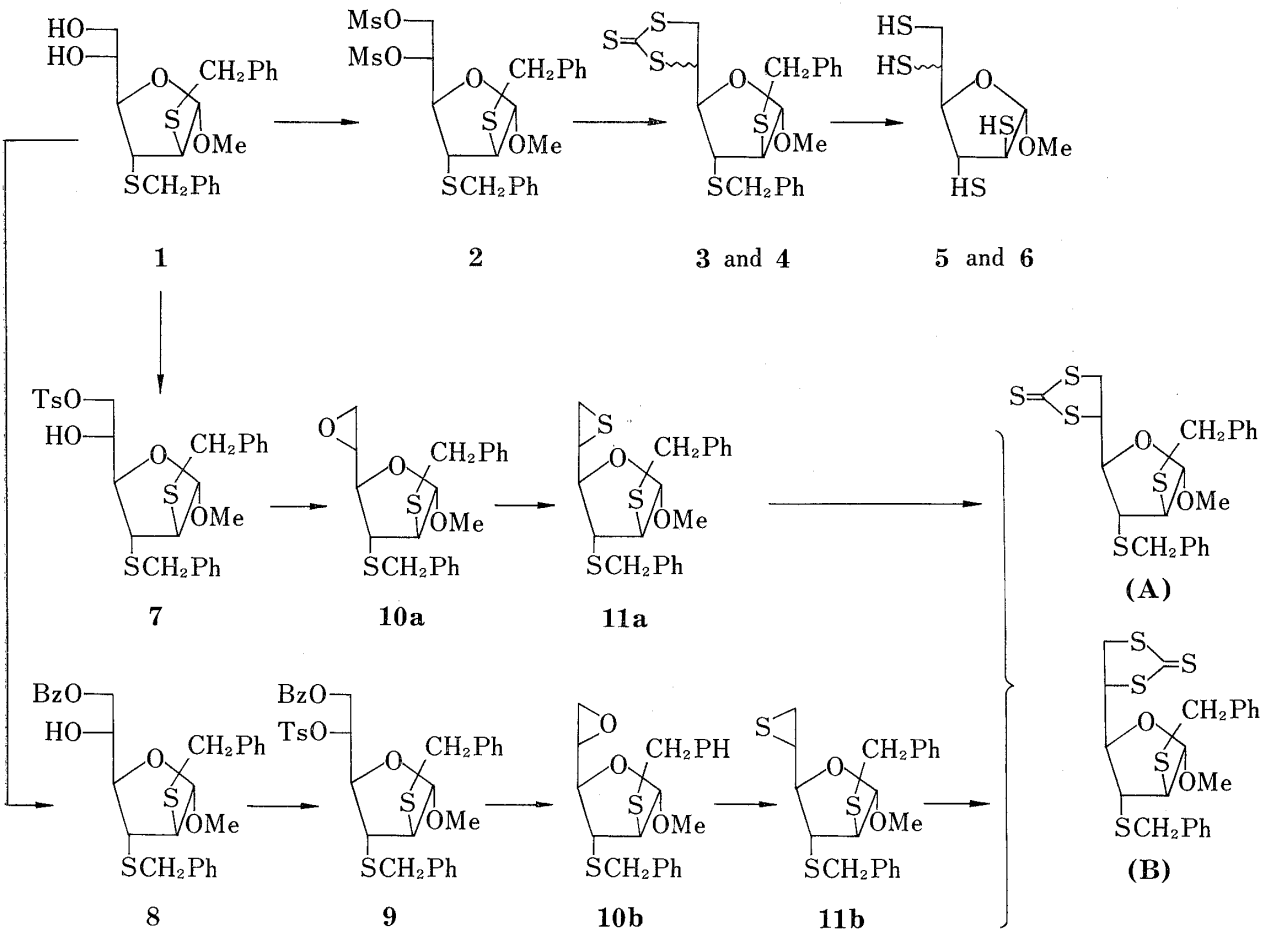

Ms: methanesulfonyl
Ts: toluene-*p*-sulfonyl
Bz: benzoyl

Chart 1

methyl xanthate was clarified by Owen *et al.*[9,10] and Pritchard *et al.*[11] It is known that ring opening of a terminal epoxide with thiourea or potassium methyl xanthate proceeds at the primary position to give the episulfide, accompanied by Walden's inversion at C-5, and the reaction of the terminal episulfide with potassium methyl xanthate affords a trithiocarbonate in which the configuration of C-5 is the same as that of the original episulfide. Accordingly, we attempted to determine the configuration at C-5 of the trithiocarbonates (**3** and **4**) by derivation of these compounds from the 5,6-epoxides (**10a** and **10b**) or 5,6-episulfides (**11a** and **11b**).

Methyl 5,6-anhydro-2,3-di-S-benzyl-2,3-dideoxy-2,3-dithio-α-D-altrofuranoside (**10a**) and -β-L-galactofuranoside (**10b**) were synthesized from **1** according to conventional procedures. Methyl 2,3-di-S-benzyl-2,3,5,6-tetradeoxy-5,6-epithio-2,3-dithio-β-L-galactofuranoside (**11a**) and -α-D-altrofuranoside (**11b**) were derived from the epoxides **10a** and **10b**, respectively, by treatment with thiourea. In the reaction of the epoxides with potassium ethyl xanthate (3 mol) in methanol, the D-5,6-epoxide (**10a**) gave **3** (5%) and **4** (39%) together with methyl 2,3-di-S-benzyl-2,3,5,6-tetradeoxy-5,6-epithio-2,3-dithio-β-L-galactofuranoside (**11a**, 9%)under reflux for 20 min. On the other hand, the L-5,6-epoxide (**10b**) gave **4** (41%) as a sole product

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Table I. Reactions of Some Thiosugars with Potassium Ethyl Xanthate

Compd.	React. time	React. temp. (°C)	Ethyl xanthate (mol)	Solvent	Yield of product (%)	
					3	**4**
2	100 hr	Reflux	1	Acetone	4.4	18.8
9	5 hr	Reflux		Methanol	13.4	32.2
10a	20 min	70	3	Methanol	5.0	39.0
10b	45 min	70	3	Methanol	—	41.2
11a	76 hr	r.t.[a]	1.5	Methanol	—	73.0
11a	30 min	70	1.5	Methanol	4.0	40.0
11b	5 hr	r.t.[a]	1.5	Methanol	—	65.0
11b	30 min	70	1.5	Methanol	—	61.0

a) r.t.: room temperature.

under reflux for 45 min. This result is not consistent with that of Owen. Thus, it was necessary to confirm whether the reaction of the epoxides (**10a** and **10b**) with potassium ethyl xanthate proceeded *via* the episulfide. In the reaction of the 5,6-episulfides (**11a** and **11b**) with potassium ethyl xanthate in methanol, the L-episulfides (**11a**) afforded only **4** in 81% yield at room temperature, but when the reaction was carried out at 70°, a small amount of **3** (3%) was obtained together with **4** (40%). On the other hand, similar reaction of **11b** gave only **4** (61—65%) at either room temperature or at 70° (Table I). There is no possibility that **3** might be derived from **4**, or that the L-episulfide (**11a**) might rearrange to the D-episulfide (**11b**). Consequently, it is difficult to determine the configuration of **3** and **4** according to Owen's principle.

Table II. Chemical Shifts of Methylene Protons of the Benzylthio Groups at C-2 and C-3

Compound	Chemical shift (δ)[a]
10a	3.73 (2H, s), 3.83 (2H, s)
10b	3.78 (4H, s)
11a	3.78 (4H, s)
11b	3.73 (2H, s), 3.82 (2H, s)
3	3.77 (1H, d), 3.88 (2H, s), 4.02 (1H, d)
4	3.68 (2H, s), 3.75 (2H, s)

a) in $CDCl_3$.

Next, we tried to determine the configurations of **3** and **4** by nuclear magnetic resonance (NMR) spectroscopy. Table II shows the chemical shifts of the methylene protons of the benzylthio groups at C-2 and C-3 of **10a**, **10b**, **11a**, **11b**, **3** and **4**. The methylene protons in **10a**, **10b**, **11a**, and **11b**, the configurations of which are known, gave the expected shifts. Thus, the signals for the methylene protons of the 2,3-dibenzylthio groups appeared as two singlets for **10a** and **11b**, belonging to the D-series, but as one singlet for **10b** and **11a**, belonging to the L-series. The spectrum of **4** showed two singlet signals due to D-series methylene protons. On the other hand, the methylene proton signals of **3** appeared as a singlet at δ 3.88 (2H) and two doublets (J_{gem}=13 Hz, AB quartet) at δ 3.77 (1H) and 4.02 (1H). This phenomenon may be explained as follows. The benzylic methylene protons of **3** should be magnetically nonequivalent due to the steric effect of the 5,6-trithiocarbonate group. In the absence of such an effect, the two doublet signals should change to a singlet at δ 3.89, overlapping the singlet signal of the C-2 benzylic methylene protons at δ 3.88. This view is supported by conformational analysis using a CPK molecular model. In all

possible conformations of the L-galactoside structure, steric hindrance of the 5,6-trithiocarbonate group on the benzylic methylene protons at C-2 and C-3 is not sufficient to produce nonequivalence. For the D-altroside structure, however, only two possible conformations are available because of the restricted rotation of 5,6-trithiocarbonate about the C_4—C_5 bond. The L_1 conformation is predominant due to the lower repulsion between the sulfur atoms at C-3 and C-5, and at C-2 and C-5, and also between the sulfur atom at C-5 and oxygen in the furanose ring. Consequently, it is suggested that the benzylic methylene protons at C-3 in the L_1 conformation give an AB quartet signal because of restricted rotation caused by the proximity of the sulfur atom at C-5. Accordingly, **3** can be assigned as methyl 2,3-di-S-benzyl-2,3,5,6-tetradeoxy-2,3-dithio-5,6-(thiocarbonyl)dithio-β-L-galactofuranoside (**B**) and **4** as methyl 2,3-di-S-benzyl-2,3,5,6-tetradeoxy-2,3-dithio-5,6-(thiocarbonyl)dithio-α-D-altrofuranoside (**A**). Treatment of the 6-O-tosylate (**7**) with potassium ethyl xanthate gave **3** in a yield of 13.4% together with **4** (32.2%).

The formation of **3** and **4** from **11a** and **11b** can be explained as follows. The ring opening of the 5,6-episulfide of **11b** by the xanthate anion proceeds normally at C-6. However, in the case of the ring opening of **11a**, some effect of the benzylthio substituents at C-2 and C-3, which is not yet apparent, may cause abnormal ring opening of the episulfide. Ring opening of the episulfide at C-5 with Walden's inversion of the L-episulfide (**11a**) affords the D-5,6-trithiocarbonate (**4**).

Reduction of **3** and **4** with liquid ammonia-metallic sodium afforded methyl 2,3,5,6-tetradeoxy-2,3,5,6-tetrathio-β-L-galactofuranoside (**5**) and methyl 2,3,5,6-tetradeoxy-2,3,5,6-tetrathio-α-D-altrofuranoside (**6**), respectively. The infrared (IR) spectra of both **5** and **6** showed the characteristic absorption (2540 cm^{-1}) of the SH group. The elemental analyses were also compatible with these structures.

Experimental

General Methods——Melting points are uncorrected. Specific rotations were measured with an automatic polarimeter (Jasco DIP-SL). IR spectra were recorded with a Jasco DS-701 instrument, and NMR spectra with JEOL JNM-C-60H and JNM-MH 100 spectrometers. Column chromatography was performed on 100 mesh silicic acid (Mallinckrodt Chem. Co.) with the specified solvent.

Methyl 2,3-Di-S-benzyl-2,3-dideoxy-5,6-di-O-methanesulfonyl-2,3-dithio-α-D-altrofuranoside (2)—— Mesylation of methyl 2,3-di-S-benzyl-2,3-dideoxy-2,3-dithio-α-D-altrofuranoside (**1**) (9.47 g) with methanesulfonyl chloride (10.67 g) in pyridine followed by column chromatography (chloroform) gave crystalline **2** (12.85 g, 96%). Recrystallization from methanol gave needles,mp 69—71.5°, $[\alpha]_D^{14}$ +110° (c=1.0, chloroform); IR ν_{max}^{Nujol} 1379 and 1175 cm^{-1}. *Anal.* Calcd for $C_{23}H_{30}O_8S_4$: C, 49.09; H, 5.37. Found: C, 49.05; H, 5.40.

Methyl 2,3-Di-S-benzyl-2,3,5,6-tetradeoxy-2,3-dithio-5,6-(thiocarbonyl)dithio-β-L-galactofuranoside (3) and -α-D-altrofuranoside (4)——a) An ethanol solution (18.8 ml) containing sodium trithiocarbonate (3.8 g) was added dropwise to a solution of **2** (7.53 g) in acetone (400 ml) with heating and stirring. The mixture was refluxed for 100 hr and concentrated *in vacuo*. Water was added to the residual syrup, and the mixture was extracted with ether. The ether was concentrated *in vacuo* to give a syrup which was eluted from silica gel with benzene. The first product was yellow crystalline **3** (285 mg, 4.4%). Recrystallization from ethanol gave yellow needles, mp 131—131.5°, $[\alpha]_D^{14}$ +195° (c=1.0, chloroform); IR ν_{max}^{Nujol} cm^{-1}: 1062 (C=S); UV $\lambda_{max}^{Dioxane}$ nm (ε): 455 (87), 319 (15900); CD (dioxane): $[\theta]_{500}$ 0, $[\theta]_{435}$ −10300, $[\theta]_{320-315}$ +28300, $[\theta]_{300}$ +36000; ORD (dioxane): $[\phi]_{485}$ −4240, $[\phi]_{420}$ +11480, $[\phi]_{333}$ +34300, $[\phi]_{289}$ −3400; NMR ($CDCl_3$) δ: 2.95 (q, 1H, $J_{2,3}$=10.2 Hz, $J_{3,4}$=7.5 Hz, H-3), 3.15 (q, 1H, $J_{1,2}$=4 Hz, $J_{2,3}$=10.2 Hz, H-2), 3.21 (s, 3H, CH_3O), 3.50 (q, 1H, $J_{5,6}$=7.5 Hz, $J_{6,6}$=12 Hz, H-6), 3.77 (d, J_{gem}=13 Hz, CH_2S), 3.88 (s, 2H, CH_2S), 4.02 (d, 1H, J_{gem}=13 Hz, CH_2S), 3.95 (t, 1H, $J_{3,4}$=7.5 Hz, $J_{4,5}$=7.5 Hz, H-4), 4.22 (sextet, 1H, $J_{4,5}$=7.5 Hz, $J_{5,6}$=7.5 Hz, $J_{5,6}$=5.5 Hz, H-5), 4.42 (d, 1H, $J_{1,2}$=4 Hz, H-1), 7.21 (s, 10H, aromatic). *Anal.* Calcd for $C_{22}H_{24}O_2S_5$: C, 55.00; H, 5.04; Found: C, 54.95; 5.14.

The second product was syrupy **4** (1.21 g, 18.8%). Purification by rechromatography gave a yellow syrup, $[\alpha]_D^{20}$ +155° (c=1.0, chloroform); IR ν_{max}^{Neat} cm^{-1}: 1062 (C–S); UV $\lambda_{max}^{Dioxane}$ nm (ε): 455 (61), 318 (12260); CD (dioxane): $[\theta]_{495}$ 0, $[\theta]_{455}$ −6030, $[\theta]_{380}$ 0, $[\theta]_{340}$ 0, $[\theta]_{320-310}$ +18600, $[\theta]_{298}$ +23000, $[\theta]_{280}$ 0; ORD (dioxane): $[\phi]_{479}$ −1830, $[\phi]_{418}$ +7260, $[\phi]_{395}$ +7110, $[\phi]_{345}$ +14000, $[\phi]_{332}$ +11400, $[\phi]_{309}$ 0, $[\phi]_{288}$ −36600; NMR ($CDCl_3$) δ: 2.62 (q, 1H, $J_{2,3}$=6 Hz, $J_{3,4}$=8 Hz, H-3), 3.22 (q, 1H, $J_{1,2}$=1.5 Hz, $J_{2,3}$=6 Hz, H-2), 3.24 (s, 3H, CH_3O), 3.51 (q, 1H, $J_{5,6}$=6.5 Hz, $J_{6,6}$=12 Hz, H-6′), 3.68 (s, 2H, CH_2S), 3.70 (q, 1H, $J_{5,6}$=7.5 Hz, $J_{6,6}$=12 Hz, H-6),

3.75 (s, 2H, CH_2S), 3.99 (q, 1H, $J_{3,4}$=8 Hz, $J_{4,5}$=6.5 Hz, H-4), 4.27 (sextet, 1H, $J_{4,5}$=6.5 Hz, $J_{5,6}$=7.5 Hz, $J_{5,6}$=6.5 Hz, H-5), 4.72 (d, 1H, $J_{1,2}$=1.5 Hz, H-1), 7.24 (s, 10H, aromatic). *Anal.* Calcd for $C_{22}H_{24}O_2S_5$: C, 55.00; H, 5.04. Found: C, 54.79; H, 5.35.

b) A mixture of **9** (511.5 mg), potassium hydroxide (512 mg), carbon disulfide (692 mg), and methanol (5 ml) was refluxed for 5 hr. Purification of the products as described above gave **3** (57.5 mg, 13.4%) and **4** (138 mg, 32.2%).

c) A mixture of **10a** (153.3 mg), potassium ethyl xanthate (170 mg), and methanol (1 ml) was heated at 65° for 20 min with occasional shaking. Purification of the products as described above gave **3** (8.8 mg, 5%), **4** (70.6 mg, 39%), and **11a** (13.7 mg, 9%). This procedure was also applied to the reaction of **10b**, **11a**, and **11b** with potassium ethyl xanthate. The results are shown in Table I.

Methyl 2,3,5,6-Tetradeoxy-2,3,5,6-tetrathio-β-L-galactofuranoside (5)——A solution of **3** (0.5 g) in dioxane (5 ml) was added dropwise to a solution of metallic sodium (0.4 g) in liquid ammonia (20 ml). The mixture was stirred for 1 hr under cooling with dry ice-acetone. After addition of chloroform (10 ml), the liquid ammonia was evaporated off. Water was added to the residue, and the solution was neutralized with dry ice, then extracted with chloroform. Concentration of the chloroform *in vacuo* gave syrupy **5** (0.265 g, 98%), which was eluted from silica gel with benzene to give a syrup. Further purification by distillation (0.05 mmHg, 130—140°) gave a colorless syrup (122 mg, 45.5%), $[\alpha]_D^{26}$ −70° (c=1.0, chloroform); IR ν_{max}^{Neat} cm^{-1}: 2540 (SH). *Anal.* Calcd for $C_7H_{14}O_2S_4$: C, 32.53; H, 5.46. Found: C, 31.96; H, 5.29.

Methyl 2,3,5,6-Tetradeoxy-2,3,5,6-tetrathio-α-D-altrofuranoside (6)——Treatment of **4** as described above gave syrupy **6** (crude yield 88%, purified yield 41%), a colorless syrup, $[\alpha]_D^{12}$ +98° (c=1.0, chloroform); IR ν_{max}^{Neat} cm^{-1}: 2542 (SH). *Anal.* Calcd for $C_7H_{14}O_2S_4$: C, 32.53; H, 5.46. Found: C, 32.60; H, 5.30.

Methyl 5,6-Anhydro-2,3-di-S-benzyl-2,3-dideoxy-2,3-dithio-α-D-altrofuranoside (10a)——Conventional treatment of **1** (1.6 g) with toluene-*p*-sulfonyl chloride (1.39 g) in pyridine (20 ml) gave a syrupy product which was eluted from silica gel with chloroform to give syrupy **7** (1.75 g, 79%); IR ν_{max}^{Nujol} cm^{-1}: 3550 (OH), 1365, 1190, 1175 (SO_2). Sodium methoxide solution (Na 100 mg) in methanol (10 ml) was added to a precooled solution of **7** in chloroform (30 ml). The mixture was left to stand for 10 min and then poured into ice-water (30 ml). The chloroform was washed with water, dried (Na_2SO_4), and concentrated. The syrupy residue was eluted from silica gel with benzene to give **10a** as a colorless syrup (751 mg, 68.2%), $[\alpha]_D^{19}$ +106° (c=1.0, chloroform). *Anal.* Calcd for $C_{21}H_{24}O_3S_2$: C, 64.92; H, 6.23. Found: C, 65.01; H, 6.32.

Methyl 2,3-Di-S-benzyl-6-O-benzoyl-2,3-dideoxy-2,3-dithio-5-O-toluene-*p*-sulfonyl-α-D-altrofuranoside (9)——Conventional treatment of **1** (2.90 g) with benzoyl chloride (1.046 g) in pyridine (30 ml) gave a syrupy product which was eluted from silica gel with chloroform to give syrupy **8** (2.35 g, 65.6%); IR ν_{max}^{Neat} cm^{-1}: 3350 (OH) and 1725 (C–O). Treatment of **8** (2.35 g) with toluene-*p*-sulfonyl chloride (in excess) gave a syrupy product which was eluted from silica gel with chloroform to give **9** as a colorless syrup (3.26 g, quantitative yield). *Anal.* Calcd for $C_{35}H_{36}O_7S_3$: C, 63.35; H, 5.42. Found: C, 63.41; H, 5.78.

Methyl 5,6-Anhydro-2,3-di-S-benzyl-2,3-dideoxy-2,3-dithio-β-L-galactofuranoside (10b)——Sodium methoxide solution (Na 150 mg) in methanol (15 ml) was added to a precooled solution of **9** (1.12 g) in chloroform (20 ml). The mixture was left to stand for 2 hr and then poured into ice-water (20 ml). The chloroform was washed with water, dried (Na_2SO_4), and concentrated. The syrupy residue was eluted from silica gel with chloroform to give **10b** as a colorless syrup (0.89 g, 44.4%), $[\alpha]_D^{20}$ +194.1° (c=1.0, chloroform). *Anal.* Calcd for $C_{21}H_{24}O_3S_2$: C, 64.92; H, 6.23. Found: C, 64.99; H, 6.40.

Methyl 2,3-Di-S-benzyl-2,3,5,6-tetradeoxy-5,6-epithio-2,3-dithio-β-L-galactofuranoside (11a)——Thiourea (91.4 mg) was added to a solution of **10a** (235 mg) in methanol (6 ml). The mixture was stirred at room temperature for 24 hr. After addition of water, the mixture was extracted with chloroform. The chloroform was worked up as usual to give a syrupy product which was eluted from silica gel with benzene to give **11a** as a colorless syrup (240 mg, 91%), $[\alpha]_D^{23}$ +149.2° (c=1.0, chloroform). *Anal.* Calcd for $C_{21}H_{24}O_2S_3$: C, 62.34; H, 5.98. Found: C, 62.53; H, 6.05.

Methyl 2,3-Di-S-benzyl-2,3,5,6-tetradeoxy-5,6-epithio-2,3-dithio-α-D-altrofuranoside (11b)——Treatment of **10b** (97.8 mg) as described in the preparation of **11a** gave **11b** as a colorless syrup (84 mg, 84%), $[\alpha]_D^{23}$ +57° (c=1.0, chloroform). *Anal.* Calcd for $C_{21}H_{24}O_2S_3$: C, 62.34; H, 5.98. Found: C, 62.53; H, 6.09.

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